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January 22, 2002

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FROM

SENDER	EMAIL	TELEPHONE	FAX
Jeff Beno	Jbeno@Brobeck.com	(858) 720-2630	(858) 720-2555

MESSAGE

RE: U.S. Patent Application Serial No.: 09/978,454
Filing Date: October 15, 2001

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Jeff Beno	Jbeno@Brobeck.com	(858) 720-2630	(858) 720-2555

MESSAGE

RE: U.S. Patent Application Serial No.: 09/978,454
Filing Date: October 15, 2001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	**Group Art Unit: 1619**
Mark D. Erion, et al.	**Examiner: To be assigned**
Serial No.: 09/978,454	
Filed: October 15, 2001	
For: NOVEL PRODRUGS FOR PHOSPHORUS-CONTAINING COMPOUNDS	

TRANSMITTAL LETTER

Commissioner for Patents
Washington, D.C. 20231

Sir:

Enclosed are the following documents:

- First Preliminary Amendment; and
- Associate Power of Attorney.

CERTIFICATE OF TRANSMISSION
(37 C.F.R. §1.8)

I hereby certify that this paper (along with anything referred to as being attached or enclosed) is being facsimile transmitted to the United States Patent and Trademark Office on the date shown below.

JEFF BENO
Name of Person Transmitting Paper

JANUARY 22, 2002
Date of Transmission

Signature of Person Transmitting Paper

No fee is believed due with this submission; however, the Commissioner is authorized to charge any fee required or to credit any overpayment to our Deposit Account No. **50-1273**.

Respectfully submitted,

BROBECK, PHLEGER & HARRISON LLP

Dated: 1/22/02

By: Jessica R. Wolff
Jessica R. Wolff
Reg. No. 37,261

JRW:jxb

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In re the Application of:	**Group Art Unit: 1619**
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ASSOCIATE POWER OF ATTORNEY

Commissioner for Patents
Washington, D.C. 20231

Sir:

The undersigned attorney in this application hereby appoints Cynthia H. O'Donohue, Registration No. 44,980, of Metabasis Therapeutics, Inc., 9390 Towne Centre Drive, San Diego, California 92121, Telephone (858) 587-2770, to transact all business in the Patent and

CERTIFICATE OF TRANSMISSION
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JANUARY 22, 2002
Date of Transmission

Signature of Person Transmitting Paper

Trademark Office in connection with the above-identified application.

Respectfully submitted,

BROBECK, PHLEGER & HARRISON LLP

Dated: 1/22/02

By: Jessica R. Wolff
Jessica R. Wolff
Reg. No. 37,261

JRW:jxb

BROBECK, PHLEGER & HARRISON LLP
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Erion et al.	
Serial No.: 09/978,454	Group Art Unit: 1619
Filed: October 15, 2001	Examiner: To Be Assigned
Title: NOVEL PRODRUGS FOR PHOSPHORUS-CONTAINING COMPOUNDS	

Commissioner for Patents
Washington, D.C. 20231

FIRST PRELIMINARY AMENDMENT

Dear Sir:

Prior to examination of the subject application, Applicants request that the Examiner enter the following amendments. It is believed that no additional fee is due for filing this amendment. If, however, any fee should become due or credit become payable during the pendency of these proceedings, the Examiner is authorized to charge or credit the same to deposit account number 50-1273.

AMENDMENTS

In the Claims

Please cancel claim 1.

Please add new claims as follows:

--2. (New) A pharmaceutical composition comprising a compound of Formula I:

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JANVARY 22, 2002
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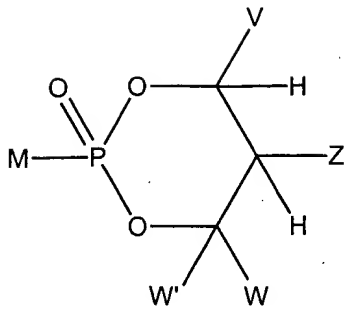

Formula I

wherein:

V, W and W' are independently selected from the group consisting of hydrogen, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, wherein the cyclic group optionally contains one heteroatom and is substituted with a hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy group attached to a carbon atom that is three atoms away from both oxygen atoms that are attached to the phosphorus atom; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group wherein the cyclic group optionally contains one heteroatom, and is fused to an aryl group, at the beta and gamma position to the oxygen attached to the phosphorus; or

together V and W are connected via an additional three carbon atoms to form an optionally substituted cyclic group containing six carbon atoms and is optionally substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy groups, wherein such substituent is attached to one of said carbon atoms that is three atoms away from an oxygen attached to the phosphorus atom; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

Z is selected from $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$(aryl), $-CH$(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OC(O)R^3$, $-OCO_2R^3$, $-SC(O)R^3$, $-SCO_2R^3$,

$-NHC(O)R^2$, $-NHCO_2R^3$, $-CH_2NH(aryl)$, $-(CH_2)_pOR^{12}$, and $-(CH_2)_pSR^{12}$;

R^2 is selected from the group consisting of R^3 and hydrogen;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^{12} is selected from the group consisting of hydrogen, and lower acyl; and

p is an interger 2 or 3;

with the provisos that:

a) V, Z, W, and W' are not all hydrogen; and

b) when Z is $-R^2$, then at least one of V, W, and W' is not hydrogen, alkyl, aralkyl, or alicyclic; and

M is selected from the group that, attached to PO_3^{2-}, $P_2O_6^{3-}$, or $P_3O_9^{4-}$, is biologically active *in vivo* and that is attached to the phosphorus atom in Formula I via a carbon, oxygen, or nitrogen atom, with the proviso that M-PO_3^{2-} is not an FBPase inhibitor;

wherein said compound of Formula I is converted to MPO_3H_2 by human liver microsomes;

pharmaceutically acceptable salts of Formula I;

and a pharmaceutically acceptable excipient.

3. (New) The pharmaceutical composition of claim 2, wherein MH is 9-(2-phosphonylmethoxyethyl)adenine (PMEA) or analogues thereof.

4. (New) The pharmaceutical composition of claim 2, wherein MH is 9-(2-phosphonylmethoxyethyl)adenine (PMEA).

5. (New) The pharmaceutical composition of claim 2, wherein MH is selected from penciclovir, 3TC, ACV, PMPA, araC, ribavirin, and 5-fluoro-2'-deoxyuridine.

6. (New) The pharmaceutical composition of claim 2, wherein MH is radiolabelled 2'-deoxy-5-Iodouridine.

7. (New) The pharmaceutical composition of claim 6 wherein MH is 2'-deoxy-5-^{131}I-iodouridine.

8. (New) The pharmaceutical composition of claim 2, wherein V is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl.

9. (New) The pharmaceutical composition of claim 2, wherein the prodrug is in the *cis* configuration.

10. (New) The pharmaceutical composition of claim 8, wherein the prodrug is in the *cis* configuration.

11. (New) The pharmaceutical composition of Claim 5, wherein MH is araC and V is a heteroaryl group.

12. (New) The pharmaceutical composition of claim 11, wherein V is 4-pyridyl.--

REMARKS

Claim 1 is pending. Upon entry of this First Preliminary Amendment, claims 2-12 will be pending. Support for these new claims can be found throughout the originally filed specification. For example, support can be found where noted in the following table:

Claim	Support
2	Originally Filed Claim 95; Page 128, line 17, to page 132, line 10
3	Pages 38-39
4	Originally Filed Claim 98; page 39
5	Page 37, line 30, to page 38, line 14
6	Page 39, line 22; page 42, lines 19-23
7	Page 42, lines 19-23
8	Originally Filed Claim 95
9	Page 57, lines 18-20
10	Page 57, lines 18-20
11	Page 68, lines 20-23
12	Page 68, lines 20-23

Respectfully Submitted,

Erion et al.

Date: 1/22/02

By: Jessica R. Wolff

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